Clinical Case Reports: Open Access

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OPEN ACCESS JOURNALS

Case Report | Vol 7 Iss 1
ISSN: 2582-5038
https://dx.doi.org/10.46527/2582-5038.287

Case Report: Usher Syndrome Type II and Congenital Oculomotor Nerve Palsy

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Received: January 06, 2024; **Accepted:** February 11, 2024; **Published:** February 18, 2024

Abstract

Usher syndrome (USH) is an autosomal recessive disease characterized by congenital hearing impairment and retinitis pigmentosa. Three subtypes of Usher syndrome have been reported, each represented by different levels and onset of hearing loss, vestibular areflexia, and retinitis pigmentosa (RP). We reported a case of 47-year-old woman with USH2A gene mutation also affected by right hypotropia and partial palsy of the superior branch of the right cranial nerve III. This disease association represented a real challenge for rehabilitative management, moreover significantly worsened the patient's quality of life.

Keywords: ***Usher syndrome; Retinitis pigmentosa; Oculomotor palsy; Orthoptic; III cranial nerve***

1. Introduction

Usher syndrome (USH) is a genetic autosomal recessive disorder characterized by congenital and bilateral sensorineural hearing loss, retinitis pigmentosa (RP), and vestibular areflexia, with different entities and onset [1]. With an estimated prevalence of approximately 1/10.000 (~ 400.000 people worldwide) [1], it is the most common cause of deafness and blindness, and it is responsible for half of all cases of combined auditory and visual defects [2-4].

RP is a progressive, bilateral, symmetric retinal disease characterized by degeneration of the photoreceptors (rods and cones) or retinal pigment epithelium, which leads to progressive visual loss [5]. RP affects 1 in 3000-7000 people in the United States [6-8].

Typical RP is also described as a “rod-cone dystrophy,” where rods are more affected than cones: retinal degeneration starts in the mid-periphery, advancing toward the macula and fovea [5]. This explains why patients show only night blindness at first and visual impairment later in daylight. Night blindness is followed by a decrease in visual field, leading to tunnel vision. The disease progresses over years or decades to affect central vision; however, in adulthood, many people become legally blind [9,10].

The most recent classification divides USH into three distinct clinical subtypes: USH1, USH2, and USH3, based on symptom severity, progression, and age at onset [1,11]. The most common type is USH2, more than half of all cases of US [3], and it is characterized by sloping audiogram, congenital sensoneurinal hearing loss, and retinitis pigmentosa (diagnosed later than the second decade of life) [12].

Oculomotor nerve palsy is an ocular condition caused by congenital or acquired III cranial nerve damage [13].

III cranial nerve presents two fibers components: the first is the outer parasympathetic fibers, which innerves ciliary muscles and the sphincter pupillae Inner. The second is the somatic fibers, which innerves the elevator palpebrae superioris and four extraocular muscles: superior rectus, middle rectus, inferior rectus, and inferior oblique [14]. The etiology of congenital oculomotor nerve palsy varies: familiality (particularly in partial palsy with an AR inheritance), muscular aplasia/hypoplasia, birth trauma, or most often idiopathic causes.

III cranial nerve palsy, if complete, generates ptosis and ophthalmoplegia; otherwise, if partial, involves the superior division of the nerve with or without aberrant regeneration [15].

In the literature, very few studies have reported extrinsic ocular motility (EOM) disorders related to RP.

In the 1950s, Reinberg presented a case report of RP associated with ocular muscular limitations due to possible dystrophy [16].

In the 1960s, Sydney and Davidson reported occasional associations of RP, ptosis, and ophthalmoplegia with uncertain etiology. The authors defined this clinical condition as "abiotrophic ophthalmoplegia externa" and suggested applying it to ophthalmoplegia occurring in any variant of heredo-degenerative diseases [17].

We found other associations between RP, ophthalmoplegia, and ptosis in Kearns-Sayre syndrome, a rare neuromuscular disease with systemic involvement with hearing loss, cardiomyopathy, skeletal muscle myopathy, intestinal disorders, diabetes, hypoparathyroidism, and kidney insufficiency [18].

The only recent experience is a research article by the University La Sapienza in Rome, which considered 23 patients with RP. The purpose of this study was to highlight any eventual EOM abnormalities and evaluate whether they could be genetically determined, as well as retinal dystrophies. The authors demonstrated a variety of nonspecific EOM disorders, such as vertical deviation, in 50% of the cases [19].

We report a case of Usher syndrome type II with classical RP and partial congenital oculomotor palsy that has not been previously reported in the literature.

2. Case Report

A 47-year-old Caucasian woman with a US type II diagnosis (double homozygous mutation USH2A) presented to the Genetic Ophthalmology Unit at the Careggi Eye Clinic (University of Florence) complaining of severe and worsened sight since the last two months before the observation.

There was no family history of genetic diseases, and her medical history was unremarkable but the USH2A. Recent cranial MRI and neurological visits were negative (FIG. 1).

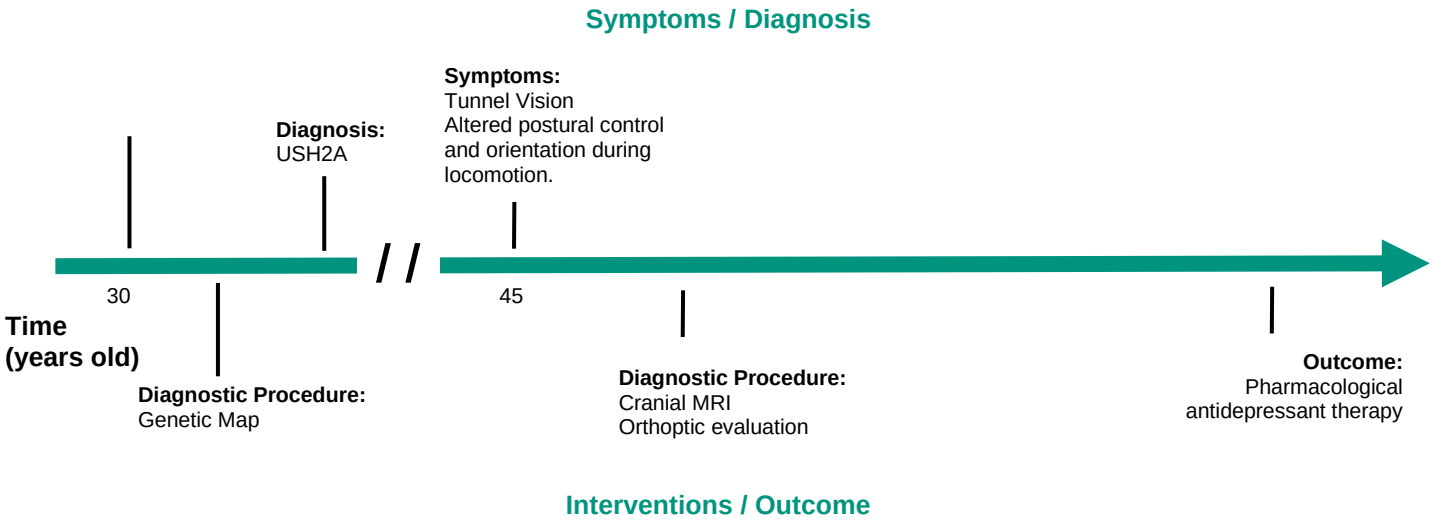

FIG. 1. **Clinical Timeline: 30-year-old, white, female diagnosed Usher Syndrome Type II. At 45 years old she referred worsened sight; we diagnose superior branch III cranial nerve palsy. USH2A=Usher Syndrome Type 2 double homozygous mutation. MRI: magnetic resonance imaging.**

Ocular history indicated that the patient denied diplopia but noted ptosis and lazy eye since childhood. The patient doesn't have long-standing head tilt consistent with the hypotropia.

She reported decreased vision since she was 30 years old, principally at night, and a progressive loss of peripheral visual field, especially during the last year.

She complained of tunnel vision, which altered postural control and orientation during locomotion. At our examination, her best-corrected visual acuity (BCVA) was 20/40 RE and 20/25 LE with -1 sph in both eyes.

Slip lamp examination showed a bilateral initial posterior subcapsular cataract. Her intraocular pressure (IOP) was 16 mmHg in both eyes. Goldmann perimetry showed a bilateral concentric constriction of the visual field, with the perception of stimulus size V/4 only inside 10° (FIG. 2).

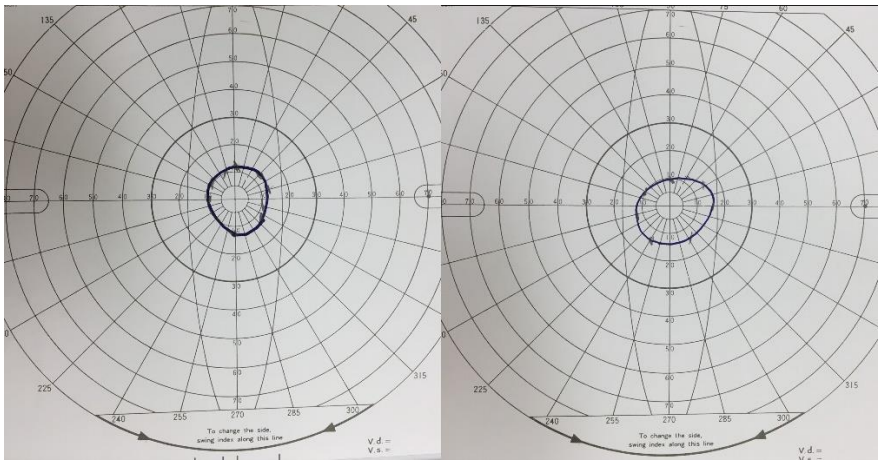

FIG. 2. **Goldmann perimetry: performed at the last visit, bilateral tubular visual field.**

Before pupillary dilatation, she underwent to an orthoptic evaluation. Corneal Reflexes (CR) shown Right hypotropia 20 PD for distance and near (FIG. 3a). She was able to maintain LE fixation for a short time, presenting a larger secondary deviation of the left hypertropia of 25 PD for distance and near (FIG. 3b). Worth 4-dot test shown suppression of the RE for both far and near and Prism Cover Test (PCT) highlight right hypotropia 35 PD at far, 30 D at near. At the Extrinsic Ocular Motility (EOM) the in the RE we found severe hypofunction of the superior rectus (SR) and hyperfunction of the inferior rectus (IR), hypofunction of the upper eyelid elevator muscle, and mild ptosis. Inferior oblique (IO) hyperfunction in the contralateral eye. Normal excursion of the bilateral horizontal recti. Small nystagmus shakes in the right lateral version.

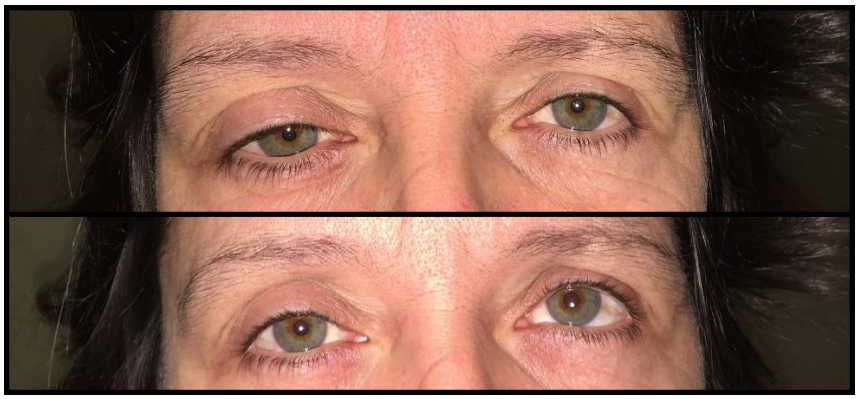

FIG. 3. **Corneal Reflex: In the upper side Corneal Reflexes fixating LE; in the lower side Corneal Reflexes fixating RE.**

Congenital partial palsy of the superior branch of the III right cranial nerve was diagnosed.

Mydriasis retinal examination revealed diffuse and widespread fine pigmentary bone spicules, which were most marked at the periphery. Optic discs (OD) were normal, and retinal vessels had a normal calibre. Optical Coherence Tomography (OCT) revealed no cystoid macular edema (CME).

Fundus autofluorescence (FAF) with the Daytona system (ultra-widefield retinal imaging technology) manifested a parafoveal ring of high density, demarcating an area of preserved central photopic function, and patchy hypoautofluorescent areas (FIG. 4). Full-field electroretinography (ERG) was performed as is usual in rod-cone dystrophy.

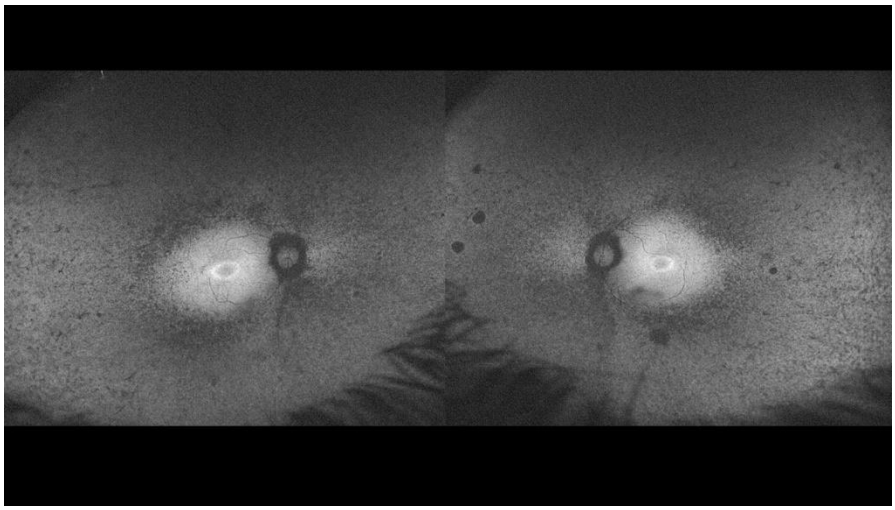

FIG. 4. **Fundus Autofluorescence: Bilateral hyperautofluorescent ring visible on Autofluorescence with Daytona system by Optos (ultra-widefield retinal imaging technology).**

3. Discussion

Retinitis pigmentosa is a very frequent retinal dystrophy associated with various systemic diseases [6]. Usher syndrome is the most frequent syndromic form, in which a typical RP is associated with sensorineural hearing loss. About 14% of all RP cases are, in fact, Usher syndroms [2,4].

Hearing loss, generally congenital and stable, may be profound, with vestibular dysfunction, ataxia, and severe visual impairment since birth (Type I). Mild/severe, with moderate hearing loss, good oral communication skills, and RP that begins in the teens and progresses throughout life characterize Type II. However, if hearing loss occurs during the first decade and worsens progressively during a lifetime, a severe stage of hearing loss is defined as Type III [2,4].

The literature describes RP peculiarities by some diagnostic criteria:

- Functional signs: hemeralopia, photophobia, and preservation of visual acuity in the early and mid-stages;
- Visual field: progressive loss of peripheral field from 30°, ring-shaped scotoma, tunnel vision;

- Anterior Segment: posterior subcapsular cataract;
- Fundus: pigmentary deposits (bone spicules) in the first stages of the peripheral retina, cystoid macular edema, attenuation of retinal vessels, waxy pallor of the optic disc, various degrees of retinal atrophy, dust-like vitreal particles
- Electroretinogram: diminution or extinction of the scotopic system in a- and b-wave amplitudes [11].

Our patient complained of hemeralopia and visual field restriction, preserving good BCVA, and she did not complain of diplopia. The ophthalmologic observation revealed the characteristic bone spicules, without CME and OD pallor. The pattern of fundus autofluorescence (FAF) matched functional tests, such as perimetry and electroretinography, delimiting a preserved area of intact photoreceptors. Orthoptic evaluation revealed partial III nerve palsy, presumably congenital, with left monovision, right suppression, and mild right ptosis.

Concerning EOM disorders in RP, literature has reported little evidence, but clinical experience demonstrates that retinal dystrophies may be related to abnormal ocular movement, primarily ascribed to genetic origins or secondary to retino-cerebral re-adjustment following visual field loss [1,14]. Loss of the peripheral visual field causes difficulties in visuo-motor coordination during locomotion; in fact, the patient usually develops compensatory mechanisms such as larger rapid-eye-movements, larger movements, and forward tilting of the head [15]. These adaptive gaze strategies require good head-eye coordination with trunk movements to minimize localization errors [15-16]. Compensatory mechanisms are the basis of rehabilitation procedures, although they may not always be effective.

In the reported case, our patient had developed typical scanning pattern vision, adapting to her tunnel vision, but complained about missing reference points for her monovision.

In fact, the absence of stereopsis and depth perception greatly worsen the perceived quality of the residual visual field. Despite the worsening of her sight and visual field, she also referred an unexpected enhancement of tactile and proprioceptive senses. In particular, she referred to an improvement in tactile feeling while keeping objects in her hands. Currently, she has many difficulties in every activity of daily living, such as walking, calculating distances, and recognizing people. For our opinion this is related to the visual field restriction.

Finally, but most importantly, the consequence of this oculomotor nerve palsy was severe strabismus and eyelid ptosis, which worsened her psychological fragility, leading to a state of psychological depression Pharmacological antidepressant therapy was prescribed because of worsening of her clinical condition.

4. Conclusion

This case report showed the association of typical inherited retinal dystrophy with an oculomotor disorder, which is also thought to be congenital in origin. To the best of our knowledge, this is the first reported case of syndromic RP complicated by inborn oculomotor nerve palsy. In conclusion, this is only a case report, but the association between inherited retinal dystrophies and ocular motor disorders should be better investigated to determine if there is any relationship between these ocular conditions to facilitate better care of these patients.

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